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Fatal Alveolar Echinococcosis of the Lumbar Spine

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For the last 10 years, the southern part of Belgium has been recognized as a low-risk area of endemicity for alveolar echinococcosis. This infection, caused by *Echinococcus multilocularis*, usually induces a severe liver condition and can sometimes spread to other organs. However, alveolar echinococcosis involving bones has been described only very rarely. Here, a fatal case of spondylodiscitis due to *E. multilocularis* contracted in southern Belgium is reported.

CASE REPORT

A 75-year-old man, a former legionnaire living in the southern part of Belgium, was referred to our institution because of deterioration in his condition despite several treatment attempts. His medical history included alcoholic liver cirrhosis, diabetes mellitus type II, and the presence of numerous nonevolutionary lung nodules, thought to be aftereffects of tuberculosis.

The patient initially came for a hospital consultation because he had been suffering from a severe pain in the lower back for a few weeks. Laboratory investigations revealed pathological values for hemoglobin (12.4 g/dl; normal values [NV], 13.3 to 17.2 g/dl), platelet count (102×10^9 /liter; NV, 150×10^9 /liter to 450×10^9 /liter), C-reactive protein (40 mg/liter; NV, ≤ 6 mg/liter), alkaline phosphatase (137 IU/liter; NV, 40 to 124 IU/liter), gamma-glutamyl transferase (66 IU/liter; NV, 5 to 50 IU/liter), gamma globulins (34%; NV, 11.1 to 18.8%), and total IgE (2,005 IU/ml; NV, 0 to 105 IU/ml). The patient's eosinophil count was within the normal range. A radiological examination confirmed the presence of an osteitis and a paravertebral abscess in the L5 region. A transbronchial biopsy of the pulmonary nodules was performed using a thin needle, and a histological examination revealed numerous necrotic granulomatous lesions, suggestive of tubercles. Thin-needle biopsies of the lumbar lesions also demonstrated the presence of several necrotic granulomas on histological examination. Bacteriological cultures including a specific medium for the growth of mycobacteria (MB/BacT system; bioMérieux, France) were performed on the pulmonary and lumbar biopsy specimens but proved negative, as did direct examination for acid-fast bacilli (AFB). A PCR specific for *Mycobacterium tuberculosis* (RealAccurate *M. tuberculosis* kit; Pathofinder, The Netherlands) was also performed on the lumbar biopsy specimens but was noninterpretable because of the presence of amplification inhibitors. In an attempt to confirm the suspected tuberculosis, surgical biopsies were performed on the L5 vertebrae and the paravertebral abscess. Histological examination again revealed the presence of granulomas, and all bacteriological cultures and microscopic examinations, including the detection of mycobacteria, remained negative. *M. tuberculosis* PCR performed on the biopsy specimens was negative (using the same method as used in the thin-needle biopsies).

However, despite the lack of laboratory evidence, an antituber-

culosis treatment combining isoniazid, rifampin, ethambutol, pyrazinamide, and moxifloxacin was initiated. During the follow-up, an *Echinococcus granulosus* serology was sent to the National Reference Laboratory and was reported strongly positive with a titer of 5,120 by indirect hemagglutination assay (IHA) using crude antigens of *E. granulosus* (ELI.H.A.; ELITech Benelux, Belgium) (NV, titer of <160). Considering this seroconversion (the same serology had been negative 1 year before), a reexamination of the biopsy specimens was carried out but did not confirm a parasitic origin of the lesions, and so this etiology was not taken into account. After 2 months of treatment, no improvement could be observed and the back pain became increasingly debilitating. Consequently, the therapy was stopped and the patient was referred to the University Hospital of Liège for further investigation.

A new imaging work-up by computed tomography (CT), magnetic resonance imaging (MRI), and 18 fluorodeoxyglucose positron emission tomography (18 FDG-PET) was carried out. CT revealed multiple well-circumscribed, roundish nodules on both lungs. Lesions showed a perivascular distribution, suggesting some hematogenous spread (Fig. 1A and B). Some of these nodules showed a central cavitation due to the erosion of the airways (Fig. 1B). No hepatic lesions were observed despite elevated hepatic enzymes, probably due to the patient's severe alcoholic liver cirrhosis, also confirmed by CT (images not shown).

CT of the lumbar spine revealed an extensive and active vertebral body osteolysis of L4 and the posterior arches of L4 and L5 vertebrae (Fig. 2A and B). MRI showed bone marrow changes of the vertebral bodies of L3 and L4 and of the posterior arches of L4 and L5, associated with a large infiltration of the nearby paravertebral soft tissues. Multiple fluid collections were detected within the abnormal soft tissue. 18 FDG-PET showed an intense and heterogeneous uptake by the distal lumbar spine, but lung lesions were not visible by this method.

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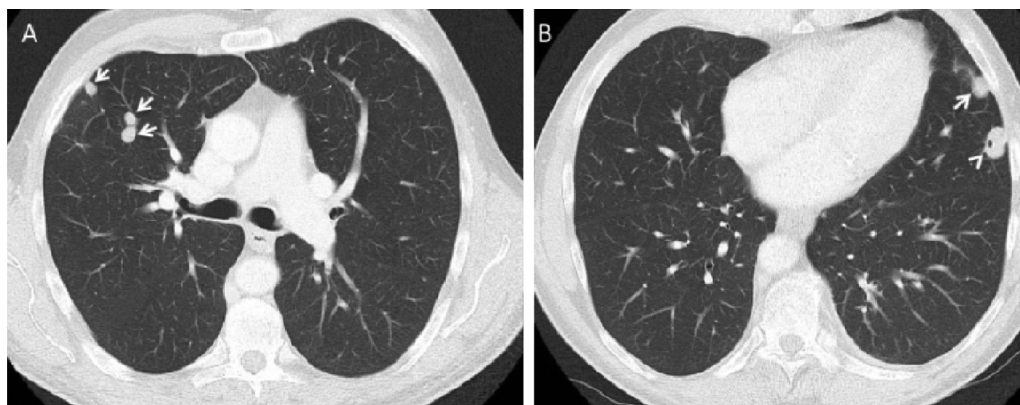


FIG 1 Chest CT shows multiple well-margined, roundish nodules with a perivascular distribution (panels A and B, white arrows) and some solid nodules with an internal cavity due to the erosion of the distal bronchioli by the nodules (panel B, white arrowhead).

Histological examination of the paravertebral abscess showed numerous cysts, ranging from 0.5 to 10 mm wide, surrounded by a severe granulomatous inflammatory reaction. In some of these cysts, there were amorphous eosinophilic membranes, staining with periodic acid-Schiff (PAS) (Fig. 3). Observation under polarized light did not reveal any specific structures (no hooklets). Again, all of the biopsy specimens were negative for bacterial cultures, including mycobacteria (Bactec MGIT 960 system; Becton, Dickinson). Microscopic examination of the lumbar biopsy specimens did not reveal any parasites: no protoscolices or hooklets were observed.

New serological samples were sent to the National Reference Laboratory in Brussels. Again, elevated antibody titers against *E. granulosus* were detected by IHA (ELI.H.A.; ELITech Benelux, Belgium) (titer of 2,560; NV, titer of <160) and also by enzyme-linked immunosorbent assay (ELISA) using a crude antigen of *E. granulosus* (in-house technique). The presence of specific antibodies against *E. multilocularis* Em2 and/or Em18 antigens was detected by ELISA, immunodiffusion (presence of two precipitin bands), and Western blotting (presence of antibodies against Em18), using in-house techniques.

Lumbar and lung biopsy specimens were sent to the Institute of Parasitology in Bern, Switzerland, where a multiplex PCR assay was performed. A 395-bp fragment specific to *E. multilocularis* was detected and led to the final diagnosis. This PCR targets mitochondrial genes for NADPH dehydrogenase subunit 1, cytochrome oxidase subunit 1, and the small subunit of rRNA of taeniids, as described by Trachsel et al. (1). The distinction between *E. granulosus*, *E. multilocularis*, and other *Taenia* spp. is based on the length of amplified products.

Although the patient was treated with albendazole (ABZ), his clinical condition deteriorated (malnutrition, pulmonary infection, liver cirrhosis, and dementia) and he died a few days after the diagnosis was established. Unfortunately, permission to carry out an autopsy was not granted by the patient's family.

Alveolar echinococcosis (AE) is caused by *E. multilocularis*, a zoonotic parasite present in the Northern Hemisphere (2–4); cystic echinococcosis is caused by *E. granulosus*, and its epidemiology differs. Infection is mainly acquired by ingestion of eggs elimi-

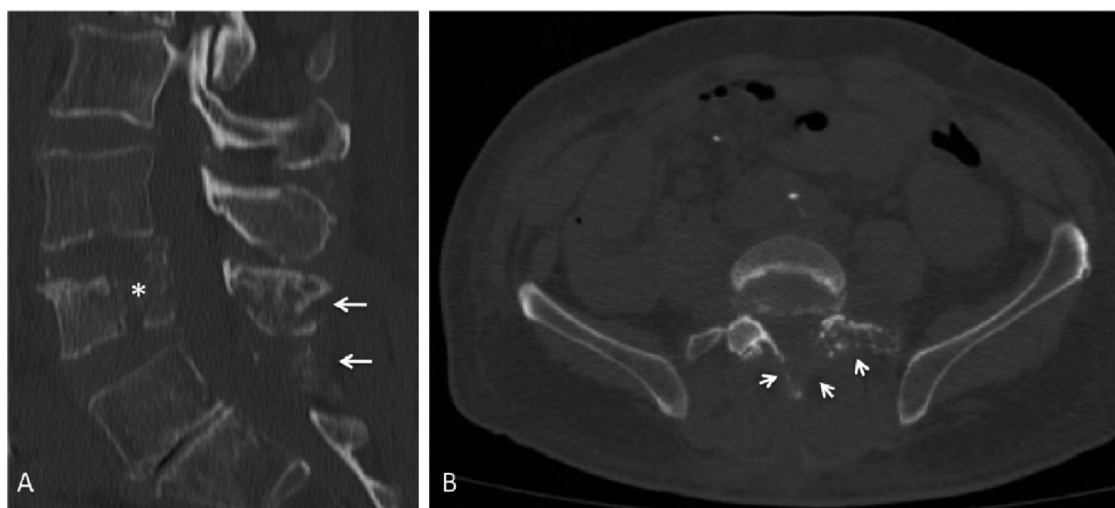


FIG 2 Sagittal and axial reformatted CT images of the lumbar spine with a massive active bone osteolysis of the posterior arches of L4 and L5 (panels A and B, white arrows) and of the vertebral body of L4 (panel A, asterisk).

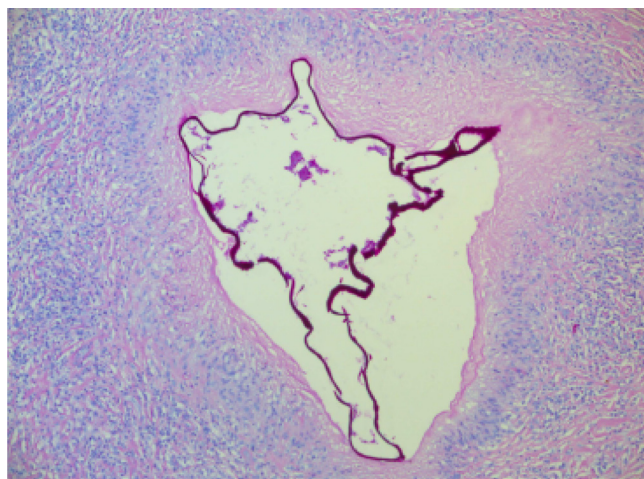


FIG 3 The histopathological examination of the paravertebral lesion shows a fibrous capsule characterized by the presence of a PAS-positive laminated layer, typical of the metacystode stage of *E. multilocularis* (PAS staining; original magnification, $\times 4$).

nated by infected foxes, such as the red fox (*Vulpes vulpes*) and the arctic fox (*Alopex lagopus*), although coyotes, domestic dogs, and wolves can also be infected (5, 6). Wild rodents are the main intermediate hosts. Additionally, humans can also become incidental hosts of the larvae. Until now, Belgium was considered to be a low-risk country for this parasitic infection. However, autopsy studies have highlighted the high rate of infection among foxes living in southern Belgium (50%), contrasting with a much lower percentage (1.7%) observed in the northern part (7, 8). Furthermore, since the first clinical case of AE was reported in southern Belgium in 2002 (9), three other case reports have been published in the same geographical area (10).

Usually, the primary infection site of *E. multilocularis* is the liver. But this parasite can develop in extrahepatic structures and infect other organs such as the pancreas, spleen, lungs, and brain. Bone infection is uncommon, occurring in up to 1% of all cases (11). Moreover, primary extrahepatic infections are extremely rare with *E. multilocularis*. Indeed, only a few cases of AE with no evidence of liver involvement have been reported in the literature (12–14). In the present case, imaging could not confirm the presence of any hepatic involvement and no biopsy was ever performed. However, numerous nodules were found in the lungs and they were probably due to the migration of the larvae from a primary, but unconfirmed, hepatic infection.

The incubation period is asymptomatic and varies from 5 to 15 years (15, 16). After this period, the symptoms of the disease generally include abdominal pain, hepatomegaly, and cholestatic jaundice due to cystic hepatic lesions. For this patient, because of his underlying liver condition, it was very difficult to relate a parasitic etiology to his hepatic disorders.

Confusion between *E. multilocularis* infection and carcinoma is common, but this was not the case here. CT findings of bone involvement due to *E. multilocularis* are not specific and led, in this case, to the confusion with tuberculosis because of the presence of granulomas at histology. At chest CT, parenchymal lesions caused by *E. multilocularis* are round or oval, dense, and well circumscribed with an intersegmental distribution. Some lung lesions may present an internal cavity. The absence of marked res-

traction of adjacent organs such as pleura, bronchi, and pulmonary vessels seems to be characteristic of AE (17). Bone abnormalities at CT consist of heterogeneous and active destructive osteolysis (18). MRI may show a diffuse infiltration and tube-like cavities/cystic lesions with a multivesicular morphology if soft tissues are involved (13, 18).

If *E. multilocularis* lesions are suspected on imaging results, the diagnosis should include a species-specific serology such as ELISA or immunodiffusion combined with Western blotting using Em2 and/or Em18 antigens (1, 19), PCR of biopsy specimens, and, if feasible or if PCR could not be done, immunochemistry (12, 20, 21). The serological tests using purified and/or recombinant Em2 antigens have a high sensitivity of 90 to 100% and a specificity of 95 to 100% (22). Because of potential cross-reactivity between the two *Echinococcus* species, the use of Em2-based serological tests should be carried out even if *E. granulosus* serology is positive, as in the present case where the patient had elevated *E. granulosus* IHA titers. Furthermore, in areas of endemicity, the use of *E. multilocularis*-specific serological tests should be recommended in the primary diagnosis tests while *E. granulosus* serology is often used as a screening assay for *Echinococcus* infection because of the availability of commercial tests.

In this case, no cystic lesions were detected in the liver but some lung and paravertebral lesions were observed. The histological examination showed typical parasitic cysts and fibrous capsules, consistent with echinococcosis. No hooklets were ever observed, consistent with the fact that in humans and other atypical intermediate hosts the germinal membrane of multilocular cysts usually does not produce protoscolices (6). In this case, *E. granulosus* serology was strongly positive and this was probably due to a cross-reaction between this species and other cestodes such as *E. multilocularis* and *Taenia solium*. A specific *E. multilocularis* serology against purified Em2 and/or Em18 antigens was clearly positive by three different serological tests, including Western blotting. Furthermore, PCR led to the detection of *E. multilocularis* nucleic acids in both paravertebral and lung biopsy specimens, confirming the definitive diagnosis of AE.

The prognosis for spinal echinococcosis is very poor. In all cases, radical surgery is the treatment of choice with total resection of the lesions. After surgery, continuous benzimidazole treatment should be given for at least 2 years to reduce the risk of recurrence (22). ABZ is the most active drug and is given at 10 to 15 mg/kg of body weight/day divided in two doses; drug monitoring is recommended at the beginning of treatment. Mebendazole can replace ABZ in the case of intolerance at a daily dose of 40 to 50 mg/kg/day divided in three doses. In the case of inoperable lesions, long-term benzimidazole treatment should be given over several years with follow-ups over a minimum of 10 years to rule out possible recurrence (22). In the case of spinal lesions, the treatment is less effective than for hepatic lesions. Untreated or inadequately treated disease presents high mortality rates. In this case, the diagnosis was delayed and ABZ treatment was not effective because of the extent of disease progression and the patient's hepatic impairment.

This case emphasizes the usefulness of species-specific PCR performed on biopsy specimens to confirm the presence of the parasite in the infected tissues. Medical doctors practicing in southern Belgium must be aware of the disease in order to make an early diagnosis that allows a rapid and curative surgical treatment.

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